REMARKS

Claims 27, 29-32, 34-37, 39-41, 43-50 and 52 are pending in the present application. Reconsideration of the application is respectfully requested in view of the following responsive remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

In the office action of April 13, 2009, the following actions were taken:

(1) The Examiner withdrew all previous rejections;

(2) Claims 27, 29-32, 34-37, 39-41, 43-50, and 52 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,602,112 (hereinafter "Rubinfeld") in view of U.S. Patent No. 6,040,294 (hereinafter "Hausheer") and further in view of U.S. Patent No. 5,227,373 (hereinafter "Alexander").

It is respectfully submitted that the presently pending claims be reconsidered and allowed. Applicants submit that each and every amendment herein, and throughout the prosecution of the present application is fully supported by the specification as originally filed, and that no new matter has been added.

Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 27, 29-32, 34-37, 39-41, 43-50, and 52 under 35 U.S.C. 103(a) as being unpatentable over several references.

The Applicant does not deem it necessary to recite the entire case law standard required in order to establish a *prima facie* case of obviousness. However, the Applicant would like to briefly remind the Examiner of the required three criteria for a *prima facie* case of obviousness, namely 1) that the asserted references as modified or combined must teach or suggest each and every element of the claimed invention, 2) that the asserted references as modified or combined must provide a sufficient likelihood of successfully making the modification or combination, and 3) that the Examiner must identify a reason for the modification or combination asserted. The recent *KSR* Supreme Court case does not change this basic analysis.

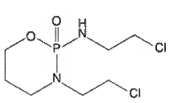
With the above background in mind, Applicants submit that the cited references do not support a *prima facie* case for obviousness.

The Applicant notes that the present claims are drawn to a process for the preparation of a low toxicity, stable oxazaphosphorine containing composition which includes mesna, an etherified β-cyclodextrin, and an oxazaphosphorine antineoplastic of a specific structure. The process involves the steps i) of adding the oxazaphosphorine antineoplastic to an aqueous solution of etherified β-cyclodextrin, ii) adding the mesna, either alone or as part of an aqueous solution containing etherified β-cyclodextrin, to the oxazaphosphorine solution, mixing the resultant solution aqueous solution, and adding water the final mixed solution such that the oxazaphosphorine antineoplastic is from 1 mg/ml to about 1000 mg/ml; the etherified β-cyclodextrin is present at a concentration of about 1% to 60% w/v; and the ratio of oxazaphosphorine antineoplastic to mesna is in the range of about 20:1 to about 1:2 on a weight basis. The Applicant submits that the present combination does not provide the instant process.

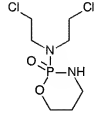
The Examiner has asserted that Rubinfeld teaches preparing a composition by adding an antineoplastic drug to a solution of 20% w/v hydroxypropylbetacyclodextrin in water. Office Action, dated 4/13/09, page 3. The Examiner notes that cyclodextrin is taught to decrease the toxicity associated with antineoplastic drugs. Office Action, dated 4/13/09, page 3. However, the Examiner admits that Rubinfeld does not teach ifosfamide or cyclophosphamide. Additionally, the Examiner admits that Rubinfeld does not teach the addition of mesna. The Examiner cites to Hausheer and Alexander as curing these deficiencies.

However, the Applicant submits that the present combination would not produce the presently claimed process. First, the Applicant agrees that Rubinfeld does not teach ifosfamide or cyclophosphamide. However, contrary to the Examiner's assertion, the Applicant submits that one skilled in the art would not assume that cyclodextrin would provide the same effects to ifosfamide or cyclophosphamide based on the disclosure of Rubinfeld since Rubinfeld only shows a handful of cytotoxic agents that achieve lowered toxicity (i.e., less ulceration and/or less vascular irritation). Specifically, the Applicant notes that Rubinfeld defines cytotoxic as "having the property of killing cells at low molar concentrations." Col. 11, lines 8-9. As such, the Applicant submits that the Examiner's interpretation would extend the benefits shown in a handful of drugs (dependent claim 2 lists 9 specific compounds) to literally tens of thousands of compounds.

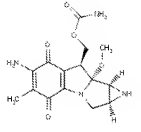
The Applicant notes that the Examiner has alleged that as Rubinfeld shows improvement in toxicity to mitomycin C, the Examiner alleges that such improvement would also extend to ifosfamide and cyclophosphamide, as all three are antineoplastic drugs (citing Hausheer). However, the Applicant respectfully disagrees. The Applicant submits that such logic could be used to say since one organic compound shows a certain effect with cyclodextrin then all organic compounds would be expected to have the same effect. However, such an argument ignores the fundamental understanding that predictability in the properties of organic compounds is low. In other words, the Applicant submits that no one skilled in the art would extend Rubinfeld's teachings to every cytotoxic compound, or even every antineoplastic drug, without some further evidence. To be clear, the Applicant notes that the difference in chemical composition between mitomycin C and ifosfamide and cyclophosphamide is significant.



Ifosfamide



Cyclophosphamide



Mitomycin C

Notably, the Applicant has not claimed a process for antineoplastic compounds but has explicitly claimed an oxazaphosphorine-containing composition. The Applicant notes that Rubinfeld does not teach or discuss any effects of cyclodextrin on oxazaphosphorine-containing compositions. As such, the Applicant submits that one skilled in the art would not assume, nor have motivation to use, ifosfamide and cyclophosphamide with the composition in Rubinfeld.

More importantly, the present claims are directed towards a process of for preparation of a low toxicity, stable oxazaphosphorine-containing composition. As such, even if the Examiner were correct in that one skilled in the art would assume that Rubinfeld's teachings applied to ifosfamide and cyclophosphamide, the Applicant has claimed a process for stabilizing ifosfamide and cyclophosphamide that is not shown in the prior art. Applicant submits that the problem to solve is how to stabilize the unstable fast deteriorating parenteral/injectable solution of

ifosfamide or cyclophosphamide in combination with mesna. Is this problem obvious from Hausheer or Rubinfeld; or both Hausheer and Rubinfeld taken together? Rubinfeld has no discussion on stability. Therefore, the Applicant submits that a person of ordinary skill in the art would have no expectation of any success from Rubinfeld process to get a stable composition of ifosfamide or cyclophosphamide and mesna based on the teachings of these cited references.

Further, the Applicant notes that Alexander teaches increased stability of ifosfamide by a completely different process. Alexander states that ifosfamide solutions are not stable. Col. 2, lines 49-51. Alexander then teaches the use of pharmaceutical lyophilizate compositions (urea) to stabilize ifosfamide. The Applicant notes that Table 1 (col. 5, lines 47-61) shows the result of various aqueous mesna/ifosfamide compositions. In conjunction with the results listed in Table 1, Alexander explicitly states that the "urea-ifosfamide compositions represent clear improvement in storage stability over the reference compositions." Col. 5, lines 43-46. The Applicant notes that the reference compositions are aqueous compositions not having urea but containing glycine or mannitol. As such, the Applicant submits that Alexander teaches away from the present process that provides a stable mesna-ifosfamide composition without the use of urea.

As the Applicant has raised the issue of teaching away, the Applicant would like to review the current case law regarding teaching away for the Examiner's convenience. The Court of Appeals for the Federal Circuit has clearly stated that "an applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." In re Petersen, 315 F.3d 1325, 1331 (Fed. Cir. 2003). The Court has also stated that "[w]e have noted elsewhere, as a 'useful general rule,' that references that teach away cannot serve to create a prima facie case of obviousness." (emphasis added) McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1354 (Fed. Cir. 2001). In identifying the appropriate standard for teaching away, the Court has further stated:

> "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be **discouraged from following the path set out in the reference**, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the

> particular facts; in general, **a reference will teach away if it suggests** that the **line of development** flowing from the reference's disclosure **is unlikely to be productive** of the result sought by the applicant." (emphasis added) In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

Clearly in the present case, a person of ordinary skill in the art would be lead in a divergent path than that taken by the Applicant; i.e., upon reading Alexander, a person of ordinary skill in the art would use urea to stabilize a mesna-ifosfamide composition. Additionally, the a person of ordinary skill in the art would be discouraged from using an aqueous composition to stabilize a mesna-ifosfamide composition since Alexander provides data that shows such compositions do not work (Table 1 – reference compounds).

Additionally, the Applicant submits that the present compositions having "the oxazaphosphorine antineoplastic is from about 1 mg/ml to about 1000 mg/ml; the etherified β-cyclodextrin in the composition is about 1% to about 60% w/v; and the ratio of oxazaphosphorine antineoplastic to mesna is in the range of about 20:1 to about 1:2 on a weight basis" would not be obvious from the present combination. As discussed above, the amount of cyclodextrin would not be attributed to the present oxazaphosphorine-containing composition. Further, the Applicant submits that the amount of these elements would not be combined in the present configuration as none of the cited references recognize that they can provide a low toxicity, stable oxazaphosphorine-containing composition. In other words, before any optimization of the ranges could be possible, the Applicant submits that a person of ordinary skill in the art would first need to recognize that they are result-effective variables for stability.

In support of this, Applicants draw the Examiner's attention to MPEP §2144.05(II)(b) which reads:

> A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie* 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

In other words, a parameter which is not already known in the art cannot be optimized. As discussed above, since the resultant composition of the claimed method was not known, it

follows that the method of the claimed invention was also not known. (Applicants note that the contrary is not necessarily true, i.e. even if the claimed composition was known, or as asserted by the Examiner, was obvious, the process of making the composition would not necessarily be known since compositions can be made by multiple processes.) In the present case, the Applicant submits that the present combination of elements would not be a matter of optimization.

In light of the above, the Applicant asserts that the Examiner has failed to set forth a *prima facie* case of obvious, and it is respectfully requested that the pending claims be allowed.

CONCLUSION

In light of the above, Applicant respectfully submits that pending claims 27, 29-32, 34-37, 39-41, 43-50 and 52 are in condition for allowance. Therefore, Applicant requests that the present rejection be withdrawn, and that the claims be allowed and passed to issue. If any impediment to the allowance of these claims remains after entry of this Amendment, the Examiner is encouraged to call Gary P. Oakeson at (801) 566-6633 so that such matters may be resolved as expeditiously as possible.

The Commissioner is hereby authorized to charge any additional fee or to credit any overpayment in connection with this Amendment to Deposit Account No. 20-0100.

DATED this 13th day of August, 2009.

Respectfully submitted,

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